PB90-261595

Cyanazine: Position Document 4. Notice of Final Determination and Intent to Cancel

(U.S.) Environmental Protection Agency, Washington, DC

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Cyanazine-containing products have exhibited teratogenic effects.

The This Position Document addresses the risks and benefits of pesticide products containing the subject active ingredient. The Agency has determined that the use of products containing the subject active ingredient may meet or exceed a risk criterion described in 40 CFR Part 154. Potential hazards will be examined further to determine the nature and extent of the risk, and considering the benefits of the subject active ingredient, whether such risks cause unreasonable adverse effects on the environment.

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PD 4

ENVIRONMENTAL PROTECTION AGENCY

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

[OPP-30000/46B; FRL]

CYANAZINE; INTENT TO CANCEL REGISTRATIONS; DENIAL OF APPLICATIONS FOR REGISTRATION; CONCLUSION OF SPECIAL REVIEW

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of Final Determination and Intent to Cancel.

SUMMARY: On April 10, 1985, EPA issued a Notice of Initiation of Special Review of registrations of pesticide products containing cyanazine. On January 7, 1987, EPA issued a Notice of Preliminary Determination announcing its preliminary determination that continued use of registered cyanazine products would be allowed only if registrants modified certain terms and conditions of registration as described herein.

This Notice concludes the Special Review of pesticide products containing cyanazine and announces EPA's final decision to cancel registrations and deny applications of all such products unless registrants make specified modifications to the terms and conditions of their registrations.

87P-1689

DATE: A request for a hearing by a registrant or applicant must be received by [insert date 30 days after date of publication in the FEDERAL REGISTER] or 30 days from receipt by mail of this Notice, whichever is the later applicable deadline. A request for a hearing from any other adversely affected person must be received by [insert date 30 days after date of publication in the FEDERAL REGISTER].

ADDRESS: Requests for a hearing must be submitted to;

Hearing Clerk (A-110),
Environmental Protection Agency,
401 M St., SW.,
Washington, DC 20460

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION: This Notice is organized into eight units. Unit I is the Introduction. It provides the background information concerning this cancellation action. Units II and III summarize the risks and the benefits associated with the use of cyanazine. Unit IV contains the comments of the Scientific Advisory Panel, the Secretary of Agriculture, and other public comments and EPA's response to those comments. Unit V describes the Agency's risk/benefit conclusions, and Unit VI describes the regulatory actions required to be complied with by this Notice. Unit VII describes the procedures which will be followed in implementing the regulatory actions EPA is announcing in this Notice. Unit VIII describes the public docket established for the Cyanazine Special Review.

I. INTRODUCTION

A. NOTICE OF SPECIAL REVIEW AND PRELIMINARY NOTICE OF INTENT TO CANCEL

On April 10, 1985, EPA issued a Notice of Special Review (also called Position Document 1 or "PD-1") on pesticide products containing cyanazine (50 FR 14151), following a finding that cyanazine met or exceeded the risk criteria in 40 CFR 162.11 (a)(3)(ii)(B), which were in effect at that time. The new, revised risk criteria which appear at 40 CFR 154.7(a)(2) are met or exceeded as well.

The Cyanazine Special Review was based on teratology studies using oral administration which showed that cyanazine produced teratogenic effects in the Fischer 344 rat [lowest-observed-effect-level (LOEL)=25 mg/kg/day, no-observed-effect-level (NOEL)=10 mg/kg/day] and fetotoxic effects in New Zealand white rabbit (LOEL=2 mg/kg/day, NOEL=1 mg/kg/day). Exposures to mixers/loaders and applicators were identified as the occupational exposures of concern.

Dermal absorption and dermal developmental toxicity studies were submitted to the Agency after the issuance of the Notice of Special Review on cyanazine. These new data led to refinement of the risk estimates presented in the Notice of Special Review. The dermal developmental toxicity study demonstrated a NOEL of 573 mg/kg/day.

Following review of public comments and available data, the Agency issued a Notice of Preliminary Determination on January 7, 1987, as well as the Cyanazine Technical Support Document. That document discussed in detail the Agency's determination regarding the risks arising from the use of cyanazine and the modifications to registration which, if adopted, would reduce risks to acceptable levels. Such modifications involved risk reduction measures and included requirements for the use of protective gloves, closed loading systems, and chemical-resistant aprons, as well as label statements regarding the cleaning of protective gloves, separate laundering of protective clothing, and the reason cyanazine has been classified for Restricted Use.

This Notice announces the Agency's intent to cancel registrations and deny applications for registration for all pesticide products that contain cyanazine as an active ingredient, unless the terms and conditions of registration are amended as described in Unit VI. This action is based on the Agency's determination that the use of cyanazine will result in unreasonable adverse effects to mixers, loaders, and applicators of cyanazine unless the required measures are adopted. A detailed discussion of the basis of this action is contained in the Notice of Preliminary Determination and the Cyanazine Technical Support Document issued on January 7, 1987 (52 FR 589). This Notice constitutes the final Agency action on the Special Review of cyanazine pesticide products initiated by the results of the developmental toxicity studies discussed herein.

B. LEGAL BACKGROUND

In order to obtain a registration for a pesticide under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended, an applicant for registration must demonstrate that the pesticide satisfies the statutory standard for registration, section 3(c)(5) of FIFRA. That standard requires, among other things, that the pesticide perform its intended function without causing "unreasonable adverse effects on the environment." The term "unreasonable adverse effects on the environment" is defined under FIFRA section 2(bb) as "any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide." This standard requires a finding that the benefits of the use of the pesticide exceed the risks of use, when the pesticide is used in compliance with the terms and conditions of registration or in accordance with widespread and commonly recognized practice.

The burden of proving that a pesticide satisfies the standard for registration rests on the proponents of registration and continues as long as the registration remains in effect. Under section 6 of FIFRA, the Administrator may cancel the registration of a pesticide or require modification of the terms and conditions of registration whenever it is determined that the pesticide appears to cause unreasonable adverse effects on the environment.

In determining whether the use of a pesticide poses risks which are greater than the benefits of its use, EPA considers both possible changes to the terms and conditions of registration which can reduce risks, as well as the impacts of such modifications on the benefits of use. If EPA determines that such changes reduce risks to the level where the benefits outweigh the risks, it may require such changes be made in the terms and conditions of registration.

Alternatively, EPA may determine that no change in the terms and conditions of a registration will adequately ensure that use of the pesticide will not pose unreasonable adverse effects. In that event, the Administrator may issue a Notice of Intent to Cancel the registration or may hold a hearing to determine whether it should be cancelled under FIFRA section 6(b). In determining whether to issue such a notice, the Administrator must take into account the impact of the action on production and prices of agricultural commodities, retail food prices, and

other possible effects on the agricultural economy. At least 60 days before formally issuing such a notice, he must inform the Secretary of Agriculture in writing of the substance of the proposed actions and supply the Secretary with an analysis of the expected impact on the agricultural economy. At the same time, under FIFRA section 25(d), the Administrator is required to submit the proposal to the Scientific Advisory Panel for comment as to the impact on health and the environment of the action proposed in the cancellation notice. EPA is also required by law, where appropriate, to consult with the U.S. Department of the Interior's Office of Endangered Species to see if the proposed action may affect an endangered species.

Unless expedited procedures are employed, EPA informs the public of its proposals to issue cancellation notices so that registrants and other interested persons can also comment or provide relevant information before a final Notice of Intent to Cancel is issued. Registrants and other interested persons are invited to review the data upon which the proposal is based and to submit data and information to address whether EPA's initial determination of risk was in error. In addition to evidence relating to risks, comments may include evidence as to whether any economic, social, and environmental benefits of use of the pesticide outweigh the risks of use.

If, after reviewing the comments received, EPA decides to issue a Notice of Intent to Cancel, any adversely affected person

may request a hearing to challenge the action. In the hearing, any party opposing cancellation would have an opportunity to present evidence. Other interested parties could intervene to present evidence. At the end of the hearing, EPA would decide on the basis of the evidence presented whether or not to cancel or restrict the registration of pesticide products. If no hearing is requested, each registration would be cancelled by operation of law 30 days after receipt by the registrant or publication in the FEDERAL REGISTER of the Final Notice, whichever occurs later.

II. DETERMINATION OF RISKS

A. RISK ASSESSMENT AND RISK REDUCTION MEASURES

The Technical Support Document includes a detailed discussion of the developmental toxicity demonstrated by the cyanazine studies, which include anophthalmia, microphthalmia, skeletal variations, diaphragmatic hernia, dilated brain ventricles, and cleft palate, as well as detailed discussions of the Agency's exposure assessment and risk assessment.

The Agency's risk assessment indicates that, while the degree of risk varies depending on the use rate and the number of acres treated, the risk is unreasonable without the adoption of protective measures as specified herein.

Traditionally, the Agency prefers the use of an oral NOEL to assess the developmental toxicity hazard of dietary exposures and a dermal developmental toxicity NOEL for occupational exposures, because each NOEL provides information relative to the potential hazard posed by a pesticide from that chosen route of administration.

Based on the NOEL (573 mg/kg/day) from the dermal developmental toxicity study in rabbits and exposure estimates from a cyanazine exposure study, margins-of-safety (MOSs) were developed using the following formula:

$$\text{Margin-of-Safety (MOS)} = \frac{\text{Dermal Developmental Toxicity NOEL}}{\text{Exposure level}}$$

The Agency generally considers a MOS of less than 100 for this biological endpoint to be a matter of concern.

1. Ground boom application. The MOSs presented for ground boom application assume that the mixer/loader and applicator are the same person. The MOSs are greater than 100 for all application rates to corn, cotton, wheat fallow, and milo when protective gloves are worn during mixing and loading operations and when adjusting, repairing, or cleaning equipment, as shown in the following Table 1:

Table 1 -- MARGINS-OF-SAFETY FOR GROUND BOOM APPLICATION[1]

Applicator[2]	Corn	Cotton	Wheat Fallow	Milo
No protection[3]	7	21	11	21
Gloves[3]	670	1980	990	1980
Gloves/closed cab	4240	12730	6370	12730

1 The MOSs in this table are for the highest use rates.

2 Assumes that mixer/loader and applicator are the same person.

3 The approximately two order of magnitude difference in the MOSs between the no glove scenario and the glove scenario is a result of comparing two independent data bases and the effect of protective gloves on reducing exposure. A worker exposure study submitted by the registrant contained exposure data only for handling scenarios in which gloves were worn. This Table is not intended to imply that protective gloves can reduce total dermal exposure by two orders of magnitude.

2. Aerial application. Aerial application to corn, grain sorghum, and wheat fallow is minimal. There are no data showing that cyanazine is being applied aerially to cotton.

The MOSs for mixer/loaders during aerial use are less than 100 unless protective gloves are worn during mixing and loading operations and when adjusting, repairing, or cleaning equipment and a closed loading system is used, as shown in the following Table 2:

Table 2 -- MARGINS-OF-SAFETY FOR AERIAL APPLICATION[1]

	Grain Sorghum	Corn	Wheat Fallow
Applicator (Pilot)	320	170	250
Mixer/Loader			
No Protection (open pour)	5	2	2
Gloves (open pour)	24	11	12
Gloves/Closed System	1000	440	520

1 The MOSs in this table are for the highest use rates.

3. Chemigation. Corn is the only crop for which chemigation is listed on the label as an application method. The MOSs for chemigation are less than 100 unless protective gloves are worn during mixing and loading operations and when adjusting, repairing, or cleaning equipment, and a closed loading system is used, as shown in the following Table 3:

Table 3 -- MARGINS-OF-SAFETY FOR CHEMIGATION[1]

	Corn
Applicator	
No protection (open pour)	13
Gloves (open pour)	59
Gloves/Closed System	2490

1 The MOSs in this table are for the highest use rate.

4. Spray drift. Surrogate exposure studies were used to estimate exposure to cyanazine through spray drift. Based on these exposure estimates, the MOS for a population exposed to cyanazine by spray drift would be over 1000.

B. OTHER RISK REDUCTION MEASURES

1. Separate laundering. Secondary exposure may occur when contaminated clothes are brought home. Although data are not available to quantify such exposure, data do show that cross-contamination does occur when contaminated clothes are washed with household laundry. Washing cyanazine-contaminated clothes separately from household laundry would prevent cross-contamination of other laundry.

2. Chemical-resistant aprons. While the risk of dermal exposure to the body from leaning against tanks during mixing or loading operations (a common occurrence) and accidental spills cannot be quantified, it may be significant in light of the developmental toxicity of cyanazine. Wearing a chemical-resistant apron while mixing or loading cyanazine would reduce exposure from accidental contact or spills.

3. Washing of protective gloves. Because hands receive the largest percentage of the dermal exposure during mixing/loading, the Agency believes that protective gloves will be contaminated on the outside with cyanazine. If protective gloves are washed with soap and water after use and before being removed from the hands, the risk of exposure from contaminated gloves will be reduced.

4. Restricted Use. Cyanazine products have already been classified for Restricted Use, as stated in the cyanazine Registration Standard which was issued in January 1985. The Registration Standard stated that the reason for this Restricted Use classification was that cyanazine had been detected in ground water and surface water. Label language regarding cyanazine's developmental toxicity and detection in ground water and surface water was added to cyanazine labels in accordance with the Registration Standard, but this language was not explicitly tied to the Restricted Use requirement.

The Agency's preliminary determination proposed requiring labels to further state that cyanazine products have specifically been classified for Restricted Use because cyanazine has been found in ground water and because it has caused birth defects in laboratory animals. The Agency based that proposed requirement on the belief that the reasons a pesticide is classified for Restricted Use should be more prominently displayed on the labels so that the users and other members of the public can more readily identify these reasons.

State sponsored monitoring studies, available at the time the Registration Standard was issued, had located residues of cyanazine in wells in Iowa, Pennsylvania, Minnesota, Illinois, and Vermont. Only a small percentage of all the cyanazine samples taken were positive, at levels close to 1 part per billion (ppb). Also, the Agency Office of Water Regulations and Standards' STORET data base had reported finding cyanazine in wells. That data base included reports on 1564 samples, reporting 21 positive samples (1.3 percent), with the 85th percentile level equal to 0.2 ppb. (State agencies submit data into the STORET data base.)

To provide a more systematic evaluation of cyanazine's contamination potential, the Agency required the registrant to conduct a ground water and surface water monitoring study. Those data have now been submitted and reviewed and are summarized below.

Two study areas of two counties each were monitored in 1986. In the hydrogeologically vulnerable East Coast, Sussex County, Delaware and Worcester County, Maryland were sampled. In the moderately vulnerable Midwest study area, Champaign County, Illinois and Jones County, Iowa were studied. There were no positive results in the 400 samples (200 wells each sampled twice). These results have some consistency with the previously mentioned monitoring studies which showed 1 percent positives with findings near and less than 1 ppb.

As a result of the newly generated monitoring data and the previously available data, the Agency no longer believes that cyanazine has significant ground water contamination potential. Therefore, EPA no longer believes that ground water contamination should be a reason for classifying cyanazine for Restricted Use. Therefore, all cyanazine labels will include a statement that cyanazine products have been classified for Restricted Use only because cyanazine has caused birth defects in laboratory animals. However, because some instances of contamination were reported in the earlier studies, the Agency believes the ground water advisory statement should remain on the label.

III. DETERMINATION OF BENEFITS

A. THE EFFECT OF THE RISK REDUCTION MEASURES ON BENEFITS

The Agency expects that the risk reduction measures required in this Notice will have a negligible effect on the benefits otherwise associated with the use of pesticide products containing cyanazine. The requirements involving separate laundering, washing of gloves, and adding a statement on Restricted Use to the cyanazine label will have minimal impact on the cost of using cyanazine pesticide products. The requirements to use protective gloves and aprons will have a negligible impact on the cost of use of cyanazine products. In as much as there is not a great deal of aerial use of cyanazine and most aerial applicators already have systems which allow for some degree of closed transfer, the requirement that aerial applicators use closed loading systems is not expected to have a significant impact on the benefits associated with cyanazine use. Similarly, there is little use of cyanazine through chemigation, and the requirement that closed loading systems be used with chemigation is not expected to have a significant impact on benefits. None of the modifications are expected to prevent users from using cyanazine products wherever such products are currently used. Thus, the Agency believes that the required modifications will have a negligible impact on the benefits associated with the use of pesticide products containing cyanazine.

B. BENEFITS AND THE TYPES OF APPLICATIONS

1. Ground boom application. The largest use of cyanazine is for broadleaf and grass weed control in corn, accounting for about 95 percent of its total annual usage. Approximately 15 to 20 million acres (20 to 25 percent of the total U.S. corn acreage) of corn are treated annually with cyanazine as either the sole active ingredient or tank-mixed with other herbicides. Growers select cyanazine over other available herbicides for the following reasons: (a) it has a wide annual broadleaf and grass weed control spectrum; (b) it can be tank-mixed with a number of herbicides to broaden its weed control spectrum; (c) it has relatively short persistence in the soil; (d) it has no rotational crop restrictions; and (e) certain soil types and/or soil conditions require the use of a short residual herbicide in order to rotate to different crops. The Agency assumes that the overall impacts from cancellation of cyanazine use on corn could have significant impacts to individual users in those areas where soil conditions preclude the use of more persistent chemicals. The Agency assumes that since the costs of the required label modifications to the user are relatively low, no one who is currently using cyanazine would be kept from its use in the future. As a result, there would only be a negligible reduction in benefits in relation to those benefits which are currently realized.

Only small acreages of wheat fallow, cotton, and sorghum are treated with cyanazine in the United States. Cyanazine is used primarily where a broad spectrum of weed control is desirable without the carry-over associated with many of the more residual herbicides. As with the impact on benefits to cyanazine use on corn, the Agency also assumes that there would only be a negligible reduction in the benefits of cyanazine use of wheat fallow, cotton, and sorghum as a result of the required label modifications.

2. Aerial application. Available data indicate that approximately 70,000 acres of corn are treated aerially with cyanazine. Aerial application to grain sorghum and wheat fallow is minimal. There are no data showing that cyanazine is being applied aerially to cotton. The main benefits from aerial application are the ability to treat either a large area in a short period of time or when the soil in the fields is too wet to allow access with ground equipment. The Agency assumes that the costs resulting from the label modification which requires closed systems for transfer of cyanazine will not create significant hardship or reduction in these benefits because most aerial applicators already have systems which allow for some degree of closed transfer.

3. Chemigation. No significant usage of cyanazine through chemigation has been reported. The Agency assumes that the required label modifications will therefore have no significant effect on the benefits associated with that type of application.

IV. COMMENTS OF USDA, SAP, AND PUBLIC

A. COMMENTS FROM USDA AND AGENCY RESPONSE

In accordance with FIFRA section 6, the Agency's preliminary determination was sent to the U.S. Department of Agriculture (USDA) for comment.

Comment from USDA. USDA commented that EPA did not give a numerical estimate for the benefits of cyanazine use on corn and that EPA should examine the risks associated with cyanazine's alternatives.

Agency response. In the Cyanazine Special Review Technical Support Document, which was issued with the Agency's preliminary determination on cyanazine, the Agency assumed that the overall impacts from concellation of cyanazine on corn would be low due to the availability of registered alternatives. EPA did not conduct a quantitative estimate of the benefits of cyanazine use on corn because EPA concluded that the impacts on corn farmers will be negligible if the registrant maintains its registrations with the label modifications proposed by the Agency in its preliminary determination.

Therefore, the Agency does not expect those who use cyanazine now to stop using cyanazine and switch to an alternative herbicide because of the required modifications to cyanazine labels. However, as mentioned in the Agency's Technical Support Document for cyanazine, the following herbicides may be used as alternatives to cyanazine: alachlor; atrazine; prometryn; propachlor; fluometuron; diuron; and simazine. The risks associated with these alternatives are given in Unit IV.A.1.-7. of this notice.

1. Alachlor. Sufficient toxicity data in laboratory animals are available in the Agency to classify this pesticide under toxicity category III for acute oral and dermal exposure. This chemical does not cause eye or skin irritation.

No teratogenic effects were demonstrated when alachlor was given to pregnant rats. However, administration of alachlor to rats at 30 mg/kg/day through three successive generations produced kidney alterations in F2 and F3 offspring. A reproductive NOEL was established by the Agency at 10 mg/kg/day.

Evidence of a mutagenic effect was not demonstrated in the several assays (CHO/HGPRT, Salmonella, E. coli, and B. subtilis). Data from chronic feeding studies indicated that alachlor induced nasal turbinate tumors in rats and bronchiolar alveolar tumors in female mice. This herbicide is classified as a category B2 oncogen (probable human carcinogen) by the Agency and a consolidated Q^* (cancer potency) of 8×10^{-2} for $(mg/kg/day)^{-1}$ human equivalents has been calculated. These risks are discussed in the Agency's Conclusion of Special Review for Alachlor signed on December 14, 1987.

2. Atrazine. The available toxicity data support the classification of atrazine under toxicity category III for acute oral, dermal, and inhalation exposure. Atrazine is neither a dermal nor eye irritant.

A rat developmental toxicity study has been classified as Supplementary Data because a developmental toxicity NOEL could not be established. The LOEL was 10 mg/kg/day (lowest dose tested), based on an increased incidence of runts. A maternal NOEL was established at 10 mg/kg/day, with decreased body weight observed at 70 mg/kg/day.

A rabbit developmental toxicity study showed a NOEL of 1 mg/kg/day and a LOEL of 5 mg/kg/day for maternal toxicity, based on reduced body weight gains. The NOEL for developmental toxicity was 5 mg/kg/day and the LOEL was 75 mg/kg/day, based on increased resorptions, reduced fetal weights for both sexes, and increases in delayed ossification. The rabbit study is also classified as Supplementary Data.

In a chronic/oncogenic rat study, an increase in carcinomas of the mammary glands was observed in females fed 70, 500, or 1000 parts per million (ppm) for 2 years. There was also an increase in the incidence of fibroadenomas/carcinomas (1000 ppm) and all mammary tumors in females receiving 500 and 1000 ppm, when compared to controls. The Agency has classified atrazine as a category C carcinogen (possible human carcinogen). Mammary gland adenocarcinoma incidence data were used to estimate the Q* of atrazine. The Q* was determined to be 1.24×10^{-1} $(mg/kg/day)^{-1}$ in human equivalents.

3. Prometryn. The available toxicity data place technical prometryn under toxicity category III for acute oral and dermal, and toxicity category IV for acute inhalation exposure. There is no evidence to suggest that prometryn is a dermal or eye irritant.

A developmental toxicity NOEL was established at 72 mg/kg in rabbits but no developmental toxicity NOEL could be ascertained from a rat teratology study. Although the rat multigeneration reproduction study was classified as supplementary data, there is no suggestive evidence of an adverse effect on reproduction up to and including the highest dose tested, 5 mg/kg/day.

Chronic and oncogenicity data are insufficient to assess the oncogenic potential of prometryn.

4. Propachlor. Propachlor is moderately toxic to laboratory animals. The acute oral and dermal LD50s are classified as toxicity category III and IV, respectively. Placement of propachlor in rabbit eyes produced corneal opacity, ulceration, iris irritation, chemosis, and conjunctivitis. This herbicide is also a strong dermal sensitizing agent.

Administration of propachlor to pregnant rats did not result in developmental toxicity up to and including a dosage level of 200 mg/kg.

The reproductive and the oncogenic potential cannot be ascertained since no valid studies are available. It is noteworthy to mention that propachlor is structurally related to alachlor (discussed previously), a B2 oncogen.

5. Diuron. Diuron is classified as toxicity category III for acute oral, dermal, and inhalation exposure. It does not produce eye or skin irritation. ..

No acceptable teratology studies are available to assess the developmental toxicity potential of diuron. A multigeneration reproduction study was conducted in rats and decreased F2b and F3a offspring weights were noted at the single dose level tested (6.25 mg/kg).

No acceptable oncogenicity studies are available. However, diuron was clastogenic in an *in vivo* cytogenetic assay. Further, diuron is structurally related to linuron, a category C oncogen (possible human carcinogen).

6. Fluometuron. Sufficient data are available to suggest that fluometuron has a low acute toxicity in laboratory animals. The acute oral and dermal LD50s and the acute inhalation LC50 belong to toxicity category III. However, fluometuron produces severe dermal irritation, corneal opacity, and may cause dermal sensitization.

No data are available to assess the developmental toxicity, reproductive, chronic, mutagenic, and oncogenic potential for this herbicide.

7. Simazine. Simazine is structurally related to atrazine and cyanazine. It is relatively non-toxic to laboratory animals after acute oral exposure (toxicity category IV). However, it is moderately toxic after inhalation (toxicity category II). The 80 percent wettable powder formulation produced corneal opacity and skin irritation.

A developmental toxicity NOEL was established in rabbits at 75 mg/kg/day with decreased fetal weights and increased skeletal variations noted at the 200 mg/kg/day. In the rat, administration of 100 ppm did not exert any adverse reproductive effect.

Data are inadequate to assess the chronic toxicity, oncogenic and mutagenic potentials of simazine.

In summary, the Agency has a more complete data base for cyanazine than for most of its alternatives. The most widely used alternative to cyanazine is atrazine, which may have more

persistent residues, has been classified as a category C oncogen, and leaches through the ground at the same rate as cyanazine.

B. COMMENTS FROM SAP AND AGENCY RESPONSE

In accordance with FIFRA section 24, the Agency's preliminary determination was sent to the FIFRA Scientific Advisory Panel (SAP or Panel) for comment. An open meeting was held with the SAP on March 24, 1987 to discuss scientific issues being considered by the Agency in connection with the Special Review of cyanazine. Specifically, the Agency requested any comments that the Panel wished to make with regard to the Agency's use of the dermal developmental toxicity study to assess the hazards from dermal exposure.

1. SAP comment on maternal toxicity. The Panel believed that the dermal developmental toxicity study was an appropriate data set for determining hazards from dermal exposure. However, the Panel also believed that the toxic endpoint that should have been used was the NOEL for dermal maternal systemic toxicity (96 mg/kg/day), not dermal developmental toxicity (573 mg/kg/day). The Panel stated that developmental toxicity occurred only at doses that were maternally toxic, and maternal systemic toxicity occurred at lower exposures; thus, a lower MOS existed for adult animals than for the developing fetus.

Agency response. Oral administration of technical cyanazine induced developmental toxicity (including malformations) in rabbits and rats. From the rabbit oral developmental toxicity data, both maternal and fetal developmental toxicity NOELs were established at 1 mg/kg/day.

Dermal application of technical cyanazine produced maternal toxicity (body weight depression and food consumption reduction) at 283 mg/kg/day and above. A maternal NOEL was established at less than 96 mg/kg/day based upon dermal irritation and at 96 mg/kg/day based upon systemic effects. Developmental toxicity (delayed ossification) was found at 955 mg/kg/day and a dermal developmental toxicity NOEL was established at 573 mg/kg/day. The NOEL of 573 mg/kg/day for dermal developmental toxicity was used by the Agency to calculate risk in its preliminary determination.

A Peer Review Committee consisting of representatives from different Agency Offices met to discuss the comments raised by the SAP. The Peer Review Committee concluded that the use of the maternal NOEL from a developmental toxicity study in calculating the MOS may not be justified because:

a. In general, maternal toxicity end points determined from a developmental toxicity study (body weight, organ weight, food consumption, clinical signs) are insensitive parameters that do not reflect a true NOEL. Based upon the weight-of-evidence, determination of maternal toxicity requires scientific judgement on a case-by-case basis.

b. Developmental toxicity manifestations may or may not be associated with maternal toxicity because the mechanisms by which toxicity is manifested are different.

c. As a screening test, a developmental toxicity study is designed primarily to assess effects on the developing organism and does not allow characterization of subtle changes in systemic toxicity due to an inadequate length of exposure (10 days).

d. Manifestations of maternal systemic toxicity may result from repeated exposures whereas manifestations of developmental toxicity more likely result from a single exposure. Therefore, NOELs for maternal systemic toxicity and for developmental toxicity may not reflect comparable lengths of time during which exposure occurred.

2. SAP comment on label language. The SAP believes that the Agency is correct in requiring the label changes to reduce applicator exposure, but that it should not state that birth defects are the reason since developmental toxicity occurred at maternally toxic doses and maternal systemic toxicity occurred at lower exposures.

Agency response. The SAP recommendation relative to "maternal toxicity occurred at lower doses than developmental toxicity" applied only to the dermal developmental toxicity data. By the oral route of administration, developmental toxicity and maternal toxicity are observed at the same dose level (both NOELs are established at 1 mg/kg/day and both LOELs are established at 2 mg/kg/day). The Agency's "Guideline for the Health Assessment of Suspect Developmental Toxicants (1986)" states that "when developmental effects are produced only at maternally toxic doses, the types of developmental effects should be examined carefully, and not discounted as being secondary to maternal toxicity. Current information is inadequate to assume that developmental effects at maternally toxic doses result only from the maternal toxicity; rather, when the lowest observed effect level is the same for the adult and developing organisms, it may simply indicate that both are sensitive to that dose level."

The developmental toxicity hazard of cyanazine was demonstrated by the oral route of administration (structural abnormalities including malformations) at maternally toxic doses, (indicating that both the mothers and developing organisms may be equally sensitive to that dose level), and confirmed by the dermal route of administration (developmental delay, altered growth) at doses higher than those producing maternal toxicity. Therefore, the developmental toxicity hazard of cyanazine is still of concern and failure to state that " ... cyanazine has caused birth defects in laboratory animals ... " is not justified. Consequently, the Agency supports its original position of requiring this advisory statement on cyanazine labels.

C. COMMENTS FROM THE PUBLIC AND AGENCY RESPONSE

The only public comment submitted in response to the Agency's preliminary determination which challenged the Agency's position was submitted by the cyanazine registrant, E. I. Du Pont De Nemours Company (Du Pont). The Cyanazine Technical Support Document, which was issued with the Agency's preliminary determination, cited Shell Chemical Company, Setre Chemical Company, and R. F. Lindsey and Sons as the registrants for cyanazine. However, since the preparation of the Technical Support Document, Setre and Lindsey have voluntarily cancelled their cyanazine registrations, and Du Pont has purchased Shell's cyanazine registrations.

1. Du Pont comment on birth defects label. Du Pont believed that there was no basis for concern from exposures associated with present use labels and that the statement regarding birth defects should be removed from the label. Also, Dupont stated that maternal toxicity was always seen at doses lower than those showing fetotoxicity, and therefore, cyanazine was not a true "teratogen" and should be of no concern.

Agency response. By the dermal route of administration, structural anomalies (not malformations) are observed in rabbits at doses higher than those producing maternal toxicity. However, by the oral route of administration, manifestations of developmental toxicity, including malformations: anophthalmia/microophthalmia; dilated brain ventricles; and diaphragmatic hernia, are observed in both rabbits and rats. Although these manifestations occur at a dose level which also produces some evidence of maternal toxicity, they cannot be considered as secondary to maternal toxicity.

Current information is inadequate to assume that developmental effects at maternally toxic doses result only from maternal toxicity; rather, when the lowest effect is the same for the adult and developing organisms, it simply indicates that both are sensitive to that dose level. Therefore, the association between developmental toxicity manifestations in both rats and rabbits by the oral route of administration and cyanazine cannot be ruled out. Based upon these data, there is evidence to suggest that cyanazine is a developmental toxicant (multi-species evidence of similar findings).

Du Pont's statement, "maternal toxicity was always seen at doses lower than those showing fetotoxicity," is misleading. This is true for the dermal but not for the oral studies in which maternal toxicity and fetotoxicity occurred at the same dosage level.

2. Du Pont comment on separate laundering. Du Pont agreed that cross-contamination may occur when contaminated clothing is washed with household laundry and that separate laundering is a "prudent precaution" to take with all pesticide contaminated clothing. However, Du Pont questioned "the imposition of a requirement to launder cyanazine-contaminated clothing separately from household laundry in lieu of data specific to cyanazine." Du Pont believed that "this requirement should be added to cyanazine labels at the time this change is mandated for all pesticide labeling, unless specific data warrant otherwise."

Agency response. The Agency notes that Du Pont agrees that it would be prudent to wash cyanazine-contaminated clothing separately from household laundry. The Agency believes that by stating such on the label it is more likely that this precaution will be taken. That label language is being required to be added to cyanazine labels at this time in order to reduce potential exposure and because the Agency has just completed its review of worker exposure to this chemical.

3. Du Pont comment on chemical-resistant aprons. Du Pont disagreed with the Agency's position regarding the use of chemical-resistant aprons. In opposition to a statement which was made in the Agency's preliminary determination, Du Pont stated that there were data to quantify the risks associated with dermal exposures resulting from leaning against mixing tanks and accidental spills; Du Pont stated that the cyanazine exposure study which was used by the Agency to calculate some of the risks presented in the preliminary determination employed all common practices in mixing and loading, including leaning against the spray tanks. Also, Du Pont believed that chemical-resistant aprons were bulky and cumbersome to wear and proposed the following label language, instead of requiring the use of chemical-resistant aprons:

> In case of accidental exposure, remove contaminated clothing and wash skin thoroughly with soap and water. Replace contaminated garments with clean, freshly laundered clothing before returning to pesticide handling operations.

Agency response. The Agency has no indication that chemical-resistant aprons are difficult to wear and has imposed this requirement on other pesticide registrations. The Agency does not agree with Du Pont's proposed label language because it is unlikely that when an accidental spill occurs, a pesticide operator would be in a situation where it is convenient to immediately remove his/her clothing, put on clean clothing, and resume his/her duties.

4. Du Pont comment on Restricted Use classification. Du Pont also believed that cyanazine should be reclassified from Restricted Use to general use. Du Pont based their position on the beliefs that: cyanazine is not a teratogen in the absence of maternal effects; the Agency's requirements for additional protective clothing and closed loading systems will provide adequate occupational MOS: and recently collected ground water samples did not contain detectable residues of cyanazine or the amide metabolite SD 20258.

Agency response. The Agency agrees with Du Pont's comment that it is not appropriate to classify cyanazine for Restricted Use due to ground water concerns. As discussed in Unit II.B.4. of this Notice, new monitoring data have shown that out of 400 samples from 200 wells in two East Coast counties and two Midwest counties, no detectable levels of cyanazine were found. However, the Agency continues to believe that cyanazine poses developmentally toxic concerns and that Restricted Use is an appropriate requirement to mitigate this concern.

The Agency has found that when a pesticide is classified for Restricted Use, the pesticide operators are better educated in the proper use of a pesticide. Therefore, it is more likely that label directions will be complied with, and practices are less likely to occur which may result in unreasonable exposures to mixers/loaders or applicators. Therefore, cyanazine will remain classified for Restricted Use because of its developmental toxicity.

V. RISK/BENEFIT CONCLUSIONS

As discussed in Unit II. of this Notice, the Agency has found that there are substantial risks associated with the currently registered use patterns of pesticide products containing cyanazine. The Agency has also determined that there are modifications available that can significantly reduce these risks. The Agency has further determined in Unit III. of this Notice that adoption of these modifications will have a negligible effect on the benefits associated with the use of pesticide products containing cyanazine. The Agency therefore believes that current use patterns generally cause unreasonable adverse effects upon the environment and that cyanazine products should be cancelled unless the following modifications are made:

1. For ground boom applications, the label must require: a. the use of protective gloves; b. use of chemical-resistant aprons; c. separate laundering of cyanazine-contaminated clothes; and d. washing of protective gloves. In addition, the label

must include a statement explaining that cyanazine products have been classified for Restricted Use because cyanazine has caused birth defects in laboratory animals.

2. For aerial applications and chemigation, the label must require: a. the use of protective gloves; b. a closed loading system; c. use of chemical-resistant aprons; d. separate laundering of cyanazine-contaminated clothes; and e. washing of protective gloves. In addition, the label must include a statement explaining that cyanazine products have been classified for Restricted Use because cyanazine has caused birth defects in laboratory animals. The labels of product formulations which cannot be used in a closed loading system must contain language prohibiting the use of those formulations via aerial application and chemigation.

VI. COMPLIANCE WITH THIS NOTICE

A. DEFINITIONS

The following terms are defined for the purposes of this Unit.

1. "Manufacturer" refers to any registrant who, as defined, sells or distributes a pesticide product containing cyanazine.

2. "Distribute and sell" and grammatical variants refer to the distribution, sale, offering for sale, holding for sale, shipping, delivering for shipment, or receiving and (having so received) delivering or offering to deliver a pesticide product.

B. REQUIREMENTS FOR COMPLYING WITH THIS NOTICE

A manufacturer of any pesticide product containing cyanazine must submit an application to amend the registration of the product within 30 days of publication in the FEDERAL REGISTER or receipt of this Notice, whichever is later, to be allowed to continue to sell and distribute the product. The application must propose to amend the registration of the product to include the following terms and conditions and modifications to labeling:

a. Require the use of protective gloves when mixing or loading cyanazine or when adjusting, repairing, or cleaning equipment.

b. Require the following precaution concerning the washing of protective gloves:

Protective gloves must be washed
with soap and water after use
and before removing from the hands.

c. Require the use of closed systems in connection with aerial use and chemigation (product formulations which cannot be used in a closed loading system must prohibit aerial use and chemigation).

d. Require use of a chemical resistant apron when mixing or loading.

e. Require that all "Restricted Use" statements include a statement that cyanazine products have been classified for Restricted Use because cyanazine has caused birth defects in laboratory animals.

f. Include the following precaution concerning the washing of contaminated clothing:

> Cyanazine-contaminated clothing should be laundered separately from household laundry to prevent cross-contamination of other laundry. Heavily contaminated or drenched clothing and protective equipment must be discarded or destroyed in accordance with State and local regulations.

C. EXISTING STOCKS AND DISPOSAL PROVISIONS

Under the authority of FIFRA Section 6(a)(1), EPA will establish certain limitations on the sale, distribution and use of existing stocks of cyanazine pesticide products subject to any final cancellation notice. EPA defines the term "existing stocks" to mean any quantity of cyanazine pesticide products in the United States on the effective date of final cancellation of a cyanazine registration or on the effective date an application for amendment of registration as provided for in Section VI.B of this Notice is granted by the Agency. Such existing stocks include cyanazine products that have been formulated, packaged and labeled and are being held for shipment or release or have been shipped or released into commerce.

As stated earlier in this Notice, EPA believes certain modifications to the terms and conditions of registration are necessary in order to prevent the use of cyanazine products from causing an unreasonable adverse effect upon the environment. In order to allow for the modifications to be made or

to allow for substitution of alternative control methods, EPA will allow sale and distribution of existing stocks of cyanazine for up to six months after final cancellation or approval of an amendment to the registration. Existing stocks may be sold or distributed, by the registrant or by any other person, after this six-month period only if the stocks have been relabeled to reflect the modifications identified in this Notice.

EPA also will allow use of existing stocks for up to 1 year after final cancellation or approval of an amendment to the registration. Existing stocks may be used after this one-year period only in accordance with the modifications identified in this Notice. Any disposal of existing stocks not relabeled in accordance with this Notice must be in accordance with the requirements of the Resource Conservation and Recovery Act.

Any existing stocks provisions involved in voluntary cancellation of a cyanazine product prior to the publication of the final Notice is not affected by this provision.

VII. PROCEDURAL MATTERS

This Notice announces EPA's intent to cancel the registrations of pesticide products that contain cyanazine. This Unit explains how current registrants may apply to amend their registrations to comply with the terms and conditions discussed in Unit V. of this Notice.

Under sections 6(b) and 3(c)(6) of FIFRA, applicants, registrants, and certain other adversely affected persons are also entitled to respond to this Notice by requesting a hearing on the actions that EPA is initiating. Unless a hearing is properly requested with regard to a particular registration or application, this action will become final by operation of law.

This Unit of the Notice explains how such persons may request a hearing on EPA's final cancellation and denial Notice (and the consequences of requesting a hearing or failing to request a hearing in accordance with these procedures).

A. PROCEDURES FOR AMENDING THE TERMS AND CONDITIONS OF REGISTRATION TO AVOID CANCELLATION OR DENIAL OF APPLICATION

Registrants affected by the cancellation actions set forth in this Notice may avoid cancellation by filing for an application for an amended registration which contains the label modifications detailed in Unit VI.B. of this Notice. This appliation must be filed within 30 days of receipt of this Notice or within 30 days from the publication of this Notice, whichever occurs later. Applicants for a registration subject to this Notice must file an amended application for registration within the applicable 30-day period to avoid denial of their pending application.

Applications must be submitted to:

Robert J. Taylor,

Product Manager 25,

Registration Division (TS-767C),

Office of Pesticide Programs,
Environmental Protection Agency,
401 M St., SW.,
Washington, DC 20460,
(703-557-1800).

B. PROCEDURES FOR REQUESTING A HEARING

To contest the cancellation action set forth in this Notice, Federal registrants or applicants may request a hearing within 30 days of receipt of this Notice, or within 30 days from publication of this Notice, whichever occurs later. Any other person adversely affected by the action described in this Notice may request a hearing within 30 days of publication of this Notice in the FEDERAL REGISTER.

A registrant or other adversely affected party who requests a hearing must file the request in accordance with the procedures established by FIFRA and EPA's Rules of Practice Governing Hearings under 40 CFR Part 164. These procedures require, among other things, that all requests must identify the specific pesticide product(s) for which a hearing is requested, and that all requests must be received by the Hearing Clerk within the applicable 30-day period. Failure to comply with these requirements may result in denial of the request for a hearing. Requests for a hearing should also be accompanied by objections that are specific for each use of each pesticide product(s) for which a hearing is requested.

Requests for a hearing must be submitted to:

Hearing Clerk (A-110),
Environmental Protection Agency,
401 M St., SW.,
Washington, DC 20460.

1. Consequences of filing a timely and effective hearing request. If a hearing on the action initiated by this Notice is requested in a timely and effective manner, the hearing will be governed by EPA's Rules of Practice for hearings under FIFRA section 6 (40 CFR Part 164), as modified below. The hearing will be limited to the specific uses and specific product registrations for which the hearing is requested.

In the event of a hearing, the specific use or uses of the specific registered product which is the subject of the hearing request will not be cancelled except pursuant to an order of the Administrator at the conclusion of the hearing.

2. Consequences of failure to file in a timely and effective manner. If a hearing concerning the registration of a specific pesticide product subject to this Notice is not requested by the end of the applicable 30-day period, registration of that product will be cancelled, unless the registrant files a request for an amended registration within the statutory period provided herein. (See Unit VI of this Notice.)

If the registration of a product covered by this Notice is cancelled by operation of law, the sale and distribution of existing stocks is governed by the provisions of Unit VI of this Notice.

C. SEPARATION OF FUNCTIONS

EPA's Rules of Practice forbid anyone who may take part in deciding this case, at any stage of the proceeding, from discussing the merits of the proceeding ex parte with any party or with any person who has been connected with the preparation or presentation of the proceeding as an advocate or in any investigative or expert capacity, or with any of their representatives (40 CFR 164.7).

Accordingly, the following EPA offices, and the staffs thereof, are designated as the judicial staff to perform the judicial function of EPA in any administrative hearing arising from this Notice of Intent to Cancel: the Office of the Administrative Law Judge, the Office of the Judicial Officer, the Administrator, and the Deputy Administrator. None of the persons designated as the judicial staff may have any ex parte communication on the merits of any of the issues involved in this proceeding, with the trial staff or any interested person not employed by EPA, without fully complying with the applicable regulations.

VIII. PUBLIC DOCKET

Pursuant to 40 CFR 154.15, the Agency has established a public docket (OPP-30000/46B) for the Cyanazine Special Review. This public docket includes:

(1) This Notice.

(2) Any other notices pertinent to the cyanazine Special Review.

(3) Non-CBI documents ... copies of written comments or other materials submitted to the Agency in response to this Notice, and any other Notice, regarding cyanazine submitted at any time during the Special Review process by any person outside government.

(4) A transcript of any public meeting held by the Agency for the purpose of gathering information on cyanazine.

(5) Memoranda describing each meeting held during the Special Review process between Agency personnel and any person outside government pertaining to cyanazine.

(6) A current index of materials in the cyanazine public docket.

On a monthly basis, the Agency will distribute a compendium of indices for newly received comments and documents that have been placed in the public docket for this Special Review. This compendium will be distributed by mail to those members of the public who have specifically requested such material for this Special Review, pursuant to 40 CFR 154.15(f)(3).

Dated: 29 Dec 87

John A. Moore,
Assistant Administrator,
Office of Pesticides and
Toxic Substances

CERTIFIED TO BE A TRUE
COPY OF THE ORIGINAL
Sandra Artis